REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 35-38 are in the case.

I. THE OBVIOUSNESS REJECTION

Claims 32 and 34 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Tinti *et al.* (EP 0 443 996 A1) (Tinti). The rejection is respectfully traversed.

As claimed, there is provided a method of treating a patient for memory loss associated with aging. The method comprises administering to the patient a therapeutically effective amount of at least one of D-β-hydroxybutyric acid, acetoacetate, or a metabolic precursor or physiologically acceptable salt of D-β-hydroxybutyric acid or acetoacetate, such as to elevate the patient's blood levels of ketone bodies, defined as the sum total of D-β-hydroxybutyric acid and acetoacetate, to a therapeutic level of from 0.3mM to 20mM effective to treat the disorder. The metabolic precursor is not a hydroxybutyryl carnitine.

As will be appreciated, the claims have been amended so as to be directed to the use of metabolic precursors of D-β-hydroxybutyric acid or acetoacetate but not hydroxybutyryl carnitine disclosed by Tinti. The invention as now claimed is not rendered unpatentable by Tinti for the following reasons.

Tinti does not suggest administration of sufficient hydroxybutyryl carnitine to elevate the level of ketone bodies in the patient's blood to 0.3mM to 20mM, as required by the claimed invention. In Applicant's previously issued related patent US 6,323,237, hydroxybutyryl carnitine is disclaimed in claim 1 with regard to neurodegenerative

disorders in the light of Cavazza *et al.* US 4,346,107 cited on the front face of the '237 patent. Claim 2 of the '237 patent relates to use of metabolic precursors of D-β-hydroxybutyric acid for treating neurodegeneration, including memory loss in ageing, by raising ketone body levels to 0.3mM to 20mM.

Tinti differs from Cavazza in so far as it includes, as one option of many carnityl esters, (R)-carnityl-(R)-(3)-hydroxybutyrate, rather than Cavazza's racemate. Thus, Tinti discloses one compound that would be expected to have its butyrate component metabolized exclusively to the ketone bodies (R)-(3)-hydroxybutyrate and acetoacetate (D-β-hydroxybutyric acid being (R)-3-hydroxybutyrate).

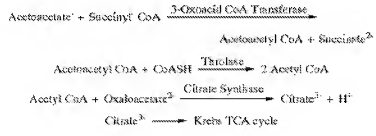
Cavazza discloses 2 to 20mg/kg to be an effective dose. Tinti similarly discloses that an effective dose of a carnityl-hydroxybutyrate is less than 10mg/kg – particularly the lead compound ST687 - isovalerylcarnityl hydroxybutyrate racemic ester (see Table). Preferred doses are stated to be 10-50mg/kg.

Published data on the efficacy of ST687 can be found in Vito Ruggiero *et al.* Mediators of Inflammation S43-S50 Vol 2 (Supplement) 1993 (see IDS submitted herewith), wherein 200mg/kg gave no benefit over 50mg/kg in TNF suppression (apparently a mechanism of that compound). In the case of ST687, less than 10mg/kg is active. Thus, there would have been no motivation based on Cavazza, Tinti and/or Ruggiero for one of ordinary skill in this art, as of the filing date of the present application, to administer greater than 50mg/kg.

Tinti also does not suggest the presently claimed invention because ST687 has a molecular formula C15H30NO6Cl, giving a molecular weight of 355.856. The molecular weight of its hydroxybutyryl component is 103.1. Thus, only 29% of the administered

material is hydroxybutyrate. As only half of this is (R)-3-hydroxybutyrate, only 14.5% by weight of ST687 is metabolized to ketone bodies. In light of this, ST687 would **not** have been a starting molecule from which to propose ketosis as the mechanism of action.

Assuming instant conversion of ST687 to ketone bodies and no concurrent metabolism therefrom to other products, it is necessary to have 0.6mM concentration of ST687 if 0.3mM of the (R)-enantiomer metabolite is to be produced. To calculate the amount of ST687 required to produce 0.3mM ketone bodies in the blood of a 70kg adult, conventionally assessed as 80% water (56 litres), the target concentration 0.6mmol is multiplied by 56litres to give the number of mmoles required as 33.6 mmol. As stated, this will have to be produced at any one time. Thus, assuming instant conversion to ketone bodies and no further metabolism therefrom, 355.8566mg/mmol x33.6mmol is required, meaning 11956.78mg or about 12g of ST687 is required. That equates to 170mg/kg just to get to the ***minimum*** specified active dose for the present invention. Those skilled in the art would immediately realize that far more than 170mg/kg would be needed to reach 0.3mM ketone bodies due to the time taken for the ST687 to be distributed and metabolized to said bodies and the concurrent further metabolism therefrom. This is illustrated particularly in Scheme 1 of US 6,316,038 where acetoacetate is metabolized to acetyl CoA:



Knowing from Cavazza, Tinti and Ruggiero that less than 10mg/Kg of ST687 is active, there would have been no motivation for one skilled in the art to administer 170mg/kg or more. Using *ex-post facto* analysis, one of ordinary skill in the art might have selected the less favored Tinti compound where X is chloride and R is hydrogen - the (R)-carnityl-(R)-(3)-hydroxybutyrate ester. That compound has a molecular weight 283.5 - requiring 283.5mg/mol x 16.8mmol to produce 0.3mM which is 4763mg or 4.76g, that is 68mg/Kg. Thus, if one selects the less favored compound and assumes it all gets absorbed instantly and does not get metabolized concurrent to uptake, the dose required is above the preferred dose and the only motivation to give more might have been that it is safe to do so. Such a disclosure is not sufficient to render the claimed invention unpatentable.

Based on the above, and in order to expedite prosecution of the present application, the claims have been amended to be directed to the use of metabolic precursors of D-β-hydroxybutyric acid or acetoacetate disclosed in the application as filed, but not encompassing use of hydroxybutyryl carnitine disclosed by Tinti. The dependent claims restrict these metabolic precursors to those not specified in the claims of already granted US 6,323,237. Withdrawal of the obviousness rejection is respectfully requested.

II. AMENDMENTS

Claim 35 has now been amended to make it clear that the disorder to be treated is memory loss associated with ageing and to reinsert the proviso present in the PCT application as filed that the precursor is not hydroxybutyryl carnitine. Claim 36 has been

further amended to recite a limited number of species for the term metabolic precursor. Support for these amendments appears in the originally filed application as follows:

- free fatty acids, the metabolism of which is through β-oxidation (paragraphs [0036-0037] as published);
- medium chain length triglycerides (paragraph [0044] as published);
- esters of D-β-hydroxybutyric acid or its oligomers with monohydric, dihydric or trihydric alcohols or acetoacetate (paragraph [0087] as published);
- wherein the monohydric, dihydric or trihydric alcohols in (iv) and (v) are selected from the group C1-C4 alkyl alcohols, (R)-1,3-butandiol and glycerol (paragraph [0093] as published).

Claim 37 relates only to use of medium chain triglycerides.

Claims 38 and 39 restrict the memory loss in ageing to that caused by Alzheimer's disease or an inability to metabolize glucose (paragraph [0014] as published). No new matter is entered.

Favorable action is awaited.

Respectfully submitted,

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